National Heart, Lung, and Blood Institute

Biologic Specimen and Data Repository

Operational Guidelines

TABLE OF CONTENTS

1.0 OVERVIEW OF THE NHLBI BIOLOGIC SPECIMEN AND DATA REPOSITORY

The National Heart, Lung and Blood Institute (NHLBI) Biologic Specimen and Data Repository is the coming together of two entities: the NHLBI Biologic Specimen Repository (NHLBI Biorepository), managed by the NHLBI, Division of Blood Diseases and Resources (DBDR), Transfusion Medicine and Cellular Therapeutics Branch, and the NHLBI Data Repository, managed by the NHLBI, Division of Prevention and Population Sciences (DPPS), Epidemiology Branch. These two programs have always had a similar mission, namely to enhance and facilitate further research in cardiovascular, pulmonary and hematologic conditions by providing access to qualified investigators to stored biospecimen and data collections. Most NHLBI-sponsored research studies have provided datasets to the NHLBI for sharing with qualified researchers, while a subset of these studies have elected to supply selected biospecimens as a shared resource. There are components of each program which do not overlap. For example, the NHLBI Biorepository maintains substantial collections from early transfusion and blood surveys, and many of these samples have only limited source characterization data rather than full epidemiological/clinical datasets. Conversely, the Data Repository maintains and distributes study datasets which do not have associated biospecimens.

One notable difference between the Data and the Biologic Specimen Repositories is that submission of data to the Data Repository is mandatory for many NHLBI-sponsored research activities, while submission of biospecimens to the NHLBI Biorepository is by application only unless otherwise designated in the sponsorship agreement.

The Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) was established under contract to the NHLBI/DBDR in September 2008. The goal of BioLINCC is to facilitate and coordinate the existing activities of the NHLBI Biorepository and the Data Repository and to expand their scope and usability to the scientific community through a single web-based user interface. BioLINCC performs the following functions in support of the shared resource:

- Develops and maintains the BioLINCC website, the central point for information on the program.
- Performs customized data-based searches for biospecimens in response to requests from outside investigators.
- Assists NHLBI-funded researchers with the application process to create new shared biospecimen collections. These services include consultation in study planning, development of the required technical/operational protocols and inclusion of appropriate ethical/legal considerations in the informed consent templates.

2.0 ACCESSING THE NHLBI BIOLOGIC SPECIMEN AND DATA REPOSITORY

2.1 INTRODUCTION

The mission of the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository is to acquire, store and distribute research biospecimens and datasets to the scientific community using the standardized processes and procedures described in this document. These resources may be accessed by qualified investigators for ethically and scientifically appropriate research that is expected to contribute to scientific discovery. Procedures used to distribute these research resources will include a Research Materials Distribution Agreement (RMDA).

The application mechanism for the acquisition of research resources, including data, biospecimens, or both, is through the BioLINCC website https://biolincc.nhlbi.nih.gov. This website allows all users to search, via keyword, for biospecimens or datasets in the Biologic Specimen and Data Repository collections. Registered website users may request additional information on specific resource availability, and conduct the entire application process and RMDA generation through the website interface.

2.2 TIMELINES FOR THE AVAILABILITY OF SHARED RESOURCES RELATED TO STUDY CONDUCT

The NHLBI Data Set policy for contracts, cooperative agreements, ancillary studies and grants reviewed after October 1, 2005 states that a shared access data set will be made available as follows:

- For Clinical Trials – No later than 3 years after the final visit of the participants to their clinical trial sites or 2 years after the main paper of the trial has been published, whichever comes first
- For Observational Epidemiology Studies – No later than 3 years after the completion of each examination or follow-up cycle or 2 years after the baseline, follow-up, genetic, ancillary study, or other data set is finalized within the study for analysis for publication, whichever comes first
- For Ancillary Studies – In those cases in which the timeline for an ancillary study differs from that of its parent study, the release date will relate to the timeline of the ancillary study.

The NHLBI Data Set Policy for contracts, cooperative agreements, ancillary studies and grants awarded prior to October 1, 2005 states that a shared access data set will be made available according to the following timelines:

- For Clinical Trials – No later than 3 years after the publication of the primary outcome paper
- For Observational Epidemiology Studies
  I. Examination Component – For data from each cycle of an examination component no later than 5 years after the last patient visit of that cycle
  II. Follow-up Component – For data from a follow-up component no later than 5 years after the last follow-up cycle cutoff date.

These timelines are also relevant to the request process for biospecimens, and they affect the procedures to obtain data related to biospecimens prior to the study end dates as defined above.

Biologic specimen collections are either in the "Proprietary Period" or the "Open Period":

"Proprietary Period" – This period lasts until the clinical study data are made available for sharing following the NHLBI Data Set sharing policy timeline. During the Proprietary Period, the BioLINCC website directs requesting researchers to the Parent Study for additional information on data and biospecimens, because that information may not yet be available to BioLINCC.

"Open Period" – This period starts when the "Proprietary Period" ends.

2.3 OVERVIEW OF THE RESEARCH RESOURCE APPLICATION PROCESS

The basic website application functionality is common across request type (datasets/biospecimens/both), regardless of whether the biospecimen collection is in the Proprietary Period or the Open Period. However, there are some key differences that requesting researchers should be aware of:

All requests for biospecimens must be approved by a panel of experts who review the following elements of the application:

- Significance and appropriateness of the proposed research
- Design of the proposed research
- Qualifications of investigator(s) to do the research
- Availability of funding
- Availability of biospecimens
- Ethical and legal considerations including consistency with the terms of the informed consent and compliance with human subjects and HIPAA regulations

Proprietary Period and Open Period biospecimen requests are processed via the website in the same manner, and require the same supporting materials. However, the main reviewing body for approval in the Proprietary Period follows the Parent Study procedures, usually through review by the Parent Study Steering Committee. The BioLINCC website is used to assemble the required documents, forward the final materials to the Parent Study for review, and notify the requesting researcher of the result of the review. BioLINCC also submits the completed packet, including Parent Study approval, to the NHLBI for final sign-off.

It should be noted that researchers wishing to obtain clinical datasets in addition to biospecimens from the Proprietary Period may need to interact with the Parent Study data center and Steering Committee, as data may not be available via BioLINCC. The BioLINCC website directs researchers to the appropriate Parent Study staff for additional information.

Open Period biospecimen requests are reviewed by the NHLBI Repository Allocation Committee (RAC). The RAC consists of three core members (two members with expertise in biospecimen collection, laboratory research, and epidemiology; and an ethicist), up to two ad hoc members from the external scientific community with expertise in the appropriate research area and one investigator from the Parent Study. NHLBI Extramural staff may not serve as reviewers on the committee but may participate in reviews to provide programmatic information.

Requests that include data from studies in the Open Period must have IRB approval (from an expedited or convened review) for the project. An IRB approval is needed since, although NHLBI

datasets have obvious identifiers removed, the wealth of individual level data remaining (demographics, anthropometry, medical history, personal history, outcomes) means that we cannot eliminate the possibility of direct identification of a study subject. Therefore, NHLBI datasets are not in the public domain and an IRB approval from an expedited (i.e., Chairman review) or full review is needed. IRB letters granting an exemption are not sufficient. Data-only requests require fewer supporting documents. However, IRB approval is required in all cases.

2.4 APPLYING FOR RESEARCH RESOURCES

The BioLINCC website https://biolincc.nhlbi.nih.gov is the interface for applications for biospecimens, associated clinical data, or both. The following tables summarize the materials and the process required to apply for each of these resource application types:

Table 1: Materials Required Based on Application Type

Requirement	Biospecimens only (including vial characterization data)	Research datasets only	Both biospecimens and associated research datasets
Summary of research plan (protocol)	Required	Required	Required
IRB review (from applicant's institution)	Full or expedited approval is acceptable; IRB statement of exemption may be appropriate in some cases	Full or expedited approval	Full or expedited approval
Curriculum vitae	Required	Required	Required
On-line request form	Required	Required	Required
Research Materials Distribution Agreement	Required; components are generated by the website automatically	Required; components are generated by the website automatically	Required; components are generated by the website automatically

Table 2: Review Process Based on Application Type

Requirement	Biospecimens only (including vial characterization data)	Research datasets only	Both biospecimens and associated research datasets
Open Period	RAC & NHLBI/DBDR	NHLBI/DPPS	RAC & NHLBI/DBDR & NHLBI/DPPS
Proprietary Period	Parent study & NHLBI/DBDR	Parent study	Parent study & NHLBI/DBDR

STEP 1 - SEARCH FOR SUITABLE RESEARCH RESOURCES

The researcher may use the BioLINCC website keyword and search functions to identify a study or studies which may have suitable research resources for the proposed study. Alternatively, the researcher may proceed directly to the target study(ies) if already known. The researcher submits a preliminary search request, specifying whether the request is for study dataset, biospecimens or both. A study protocol/proposed research plan is submitted at this time. If biospecimens are included in the request, the researcher is asked to provide more specific requirements, such as specimen material type, minimum sample volumes, and other selection criteria regarding the research subject (e.g., "male cases at baseline") or the biospecimen ("in EDTA"), as well as information on the proposed commercial/non-commercial use of the research resources. The BioLINCC staff then performs a preliminary search for suitable materials based upon the information provided in the initial request, as well as a preliminary review of data or biospecimen access restrictions based upon the type of research to be performed and any commercial use restrictions. There may be dialogue between the researcher and the BioLINCC staff to refine and finalize selections according to resource availability. For applications with a biospecimen component, vials are put on temporary hold for the requesting researcher, pending receipt of the formal resource application and approval determination. Vials that have been put on hold but which have no additional application activity for a period of six months may be released from hold without notice. If multiple researchers apply for the same research materials during the same timeframe, every effort will be made to ensure that all qualified applicants obtain sufficient biospecimens for their research; conflicts will be mediated by the Biorepository Oversight Committee (BioROC) in consultation with the Repository Allocation Committee (RAC).

STEP 2 - RESOURCE APPLICATION

Upon the finalization of the search (see STEP 1), BioLINCC creates the formal application template using the researcher-approved data and/or biospecimen criteria. The researcher appends the curriculum vitae and the IRB approval/exemption statement to the electronic application via upload. For applications with a biospecimen component, the BioLINCC staff generates a Last Vial Report based on the agreed upon selection criteria. This report provides information to the reviewing bodies regarding the impact of the request on the biospecimen inventory, specifically the number of requested vials that are the last vial of an aliquoted sample. Last vials may be subject to restricted access or to aliquoting to preserve the collection.

STEP 3 - APPLICATION REVIEW AND APPROVAL DETERMINATION

Applications are reviewed by BioLINCC and NHLBI staff to ensure their completeness. Acceptable applications with a biospecimen component are forwarded to the RAC (Open period) or Parent Study (Proprietary period) for their recommendation regarding approval, with final sign-off by NHLBI. Acceptable applications with a dataset-request component are forwarded to NHLBI/DPPS for approval (Open period). (Datasets during the Proprietary period are generally not available via BioLINCC but must be obtained directly from the Parent Study according to their conditions.) Applications which receive a Deferred or Disapproval recommendation from the reviewers may be modified at the discretion of the researcher for re-submission.

STEP 4 - REQUEST FULFILLMENT

Approved requests are fulfilled after receipt of the Research Material Distribution Agreement (RMDA), which is generated by the BioLINCC website from the final application and then must

be signed by an authorized representative of the requestor's institution. Upon receipt of the signed RMDA, the requestor is contacted by the BioLINCC staff to finalize shipping arrangements.

3.0 SUBMITTING NEW DATA AND BIOLOGIC SPECIMEN COLLECTIONS

3.1 PREPARING AND SUBMITTING DATA REPOSITORY DATASETS

The National Heart, Lung, and Blood Institute (NHLBI) has established a data repository consisting of the collected data from participants in numerous clinical trials and epidemiologic studies sponsored by the Institute. These datasets from well-characterized population samples represent rare and valuable scientific resources. In order to take full advantage of these resources and to maximize their research value, it is important that data collected with public funds be made available, under appropriate terms and conditions, to the largest possible number of qualified investigators in a timely manner. Data distribution procedures have been established and are administered by the NHLBI. These procedures require modification or elimination of data to protect participant privacy, and require that the recipient of the data sign a data distribution agreement and obtain an IRB approval from their institution prior to receipt of the data.

Guidance for researchers in the preparation of data repository datasets may be found here: https://biolincc.nhlbi.nih.gov/new_data_set_policy/

3.2 SUBMITTING BIOLOGIC SPECIMEN COLLECTIONS TO THE NHLBI BIOREPOSITORY

The NHLBI Biorepository is a shared biospecimen resource consisting of Study Collections under the custodianship of the NHLBI. Its mission is to acquire, store and distribute quality biospecimens to the scientific community using standardized processes and procedures. This resource has been managed by the Division of Blood Diseases and Resources (DBDR), Transfusion Medicine and Cellular Therapeutics Branch since the mid-1970s. During the first 20 years of operation, the NHLBI Biorepository acquired several large plasma, serum and whole blood collections from epidemiologic studies conducted among blood donors and transfusion recipients. Research on these biospecimens enabled key advancements in transfusion safety, including the evaluation of donor screening assays for viral agents as well as risk estimations for the transmission of these agents through blood-product transfusion.

In recent years, the NHLBI Biorepository has expanded to include biospecimens collected from a variety of cardiovascular, pulmonary and hematological clinical studies supported by NHLBI. The NHLBI Biorepository currently houses more than four million plasma, serum, cellular, tissue and other types of biospecimens.

In contrast to the mandated nature of the NHLBI Data Repository, the inclusion of study biospecimens in the NHLBI Biorepository is by application only, unless otherwise designated in the research support agreement. The application process is designed to assess whether a prospective collection is a sound investment of the considerable effort required to transfer and maintain it as a shared biospecimen resource. The process entails careful evaluation of the intrinsic value of the biospecimen collection and the quality and usability of the collection as highlighted here and described in more detail in Section 3.2.3.

The evaluation criteria for inclusion in the NHLBI Biorepository are as follows:

- The study collection's intrinsic value as a shared biospecimen resource based upon its uniqueness, evidence of wider scientific interest, and the usefulness of associated clinical or characterization data; and

- The demonstrated ability and willingness of the parent study to conform with Best Practices related to technical/operational and ethical/legal aspects of building a high-quality shared biospecimen resource.

3.2.1 BENEFITS OF PARTICIPATION

Applications to transfer a new Study Collection into the NHLBI Biorepository will be considered for any study funded by the NHLBI, as well as studies funded by other sources. There are numerous benefits for having a biospecimen collection accepted into the NHLBI Biorepository, including:

- Valuable specimens obtained through research efforts are made available to the wider scientific community
- Subsequent research using shared biospecimen resources must acknowledge the parent study source in publications
- Long-term storage of collections is provided in an established facility, at no charge to the researcher
- All biospecimens are inventoried and tracked in a secure centralized database, including the creation and disposition of any subsequent aliquots
- Researchers who participate in a pre-review of their proposed study methodology, as it relates to biospecimen and data collection, are eligible for custom cryolabels which are pre-printed in the required format and provided to the researcher at no charge

3.2.2 IMPORTANT CONSIDERATION

The researcher must recognize that the NHBLI Biorepository is designed to be a shared resource, and that biospecimens which are stored within this resource will ultimately be shared with others who are able to demonstrate scientifically credible research proposals as determined by the NHLBI Repository Allocation Committee (RAC). For the few collections which qualify for storage of biospecimens during the active study period, procedures are in place to restrict biospecimen access to investigators subject to parent study approval. Upon completion of the parent study and transition to the Open Period, decisions regarding sample disposition are made at the discretion of the NHLBI, under the advisement of the RAC.

3.2.3 REQUIREMENTS FOR NEW BIOLOGIC SPECIMEN COLLECTIONS - THE REVIEW PROCESS

Applicant collections will be evaluated to determine their appropriateness for inclusion in the NHLBI Biorepository. This evaluation will include two major review types:

1) A scientific review by members of the NHLBI Biorepository Oversight Committee (BioROC) to ascertain if the proposed collection meets the standards related to its Intrinsic Value as an addition to the existing collections;

   AND

2) A technological/ethical advisory review by members of the NHLBI Program Office, NHLBI Biorepository and BioLINCC to assess whether the collection meets the standards which have been set in place to ensure the quality and usability of the biospecimens themselves, along with associated clinical/research data. These standards include:

   i. the demonstrated ability of the Parent Study to develop and consistently apply standard operating procedures related to sample collection, processing, tracking, storage and shipment;
   ii. the demonstrated ability to develop, use and track required elements of Informed Consents related to collection and sharing of biospecimens and data; and
   iii. the ability to develop, maintain and submit biospecimen and data files, including files related to the linking of specimens with data.

The findings from the technological/ethical review are forwarded to the BioROC members, who then vote on the inclusion of the collection. Collections which meet the criteria for Intrinsic Value but which are unable to demonstrate adequacy in technological/ethical aspects cannot be accepted.

3.2.3.1 INTRINSIC VALUE OF NEW COLLECTION

A collection must add to the value of the existing NHLBI Biorepository collections. BioROC will determine the potential value of a proposed collection by assessing the following components:

1) Evidence of wide scientific interest
2) Absence of overlap with existing collections in terms of disease process, the nature of the collected biospecimens, or the study design
3) Associated data (clinical study and/or laboratory) which enhance the potential usefulness of the shared biospecimen resource for future research by outside investigators

3.2.3.2 REQUIRED TECHNICAL AND OPERATIONAL ASPECTS OF THE RESEARCH METHODS

1) A biospecimen collection plan must be established. The biospecimen collection plan must include information on the material types, number of biospecimens, volume and collection schedule of biospecimens to be submitted to the NHLBI Biorepository. The collection schedule may be described in any combination of text and/or flowchart. The documents should give a general overview of the anticipated or actual collection timeframes, the materials collected at each visit, the materials that will be retained for investigator use and the materials that will be submitted to the NHLBI Biorepository.

   All applications must include a summary table of the anticipated material types and quantities of biospecimens to be stored in the NHLBI Biorepository. A self-calculating table similar to the following is included on the BioLINCC website application page here: https://biolincc.nhlbi.nih.gov/static/guidelines/Aliquot_Count.xls. The table below uses the recommended aliquoting scheme, utilizing micro cryovials that are compatible with condensed storage configurations.

Table 3: Example of an Aliquot Scheme

Material type *(e.g., plasma, serum, extracted DNA, etc.)*	Aliquot volume *(e.g., 0.2 ml)*	Anticipated number of patients	Anticipated number of aliquots per patient at this volume *(combine baseline and follow-up visits)*	Calculated number of aliquots	Anticipated number of aliquots for parent study	Total number of aliquots for transfer to Biorepository
Plasma	*1ml*	*200*	*6*	*1200*	*400*	*800*
Plasma	*0.5 ml*	*200*	*4*	*800*	*200*	*600*
Serum	*1ml*	*200*	*6*	*1200*	*200*	*1000*
Serum	*0.5 ml*	*200*	*4*	*800*	*200*	*600*
Urine	*1ml*	*200*	*10*	*2000*	*1000*	*1000*
Packed Cells	*3ml*	*200*	*2*	*400*	*200*	*200*
Total specimens				*6400*	*2200*	*4200*

This information is used to determine the storage resources that would be required to house the proposed collection.

2) Acceptable Standard Operating Procedures must be in place for biospecimen collection, processing, storage and transfer. While each institution may have established standard operating procedures for the collection and processing of samples, it is imperative that a single set of standard operating procedures be used for preparing samples at each site participating in a study. The NHLBI has provided Standard Operating Procedures for the most commonly collected material types that are submitted to the repository:

   Example SOP for the Isolation and Freezing of Plasma and Packed Cells from Whole Blood

   Example SOP for the Separation and Preservation of Serum

   However, it is the responsibility of the study personnel to ensure that the procedures that are used are suitable for the potential purposes of the biospecimens. SOPs should include the following parameters:

   - Purpose - *what is the purpose of the activity being described?*
   - Scope - *what are the boundaries (extent) of the activity?*
   - Responsibility - *who are the personnel responsible for the activity?*
   - Materials Required - *what materials and supplies need to be available?*
   - Equipment Required - *what fixed equipment will be used?*
   - Detailed Procedures - *a step-by-step description of the tasks involved.*
   - Quality control checks - *a description of how and when QC will be applied.*
   - Data/Record-Keeping requirements - *template forms and a description of their use.*

3) Worksheets and forms for record-keeping of sample collection must be designed and used consistently throughout the sample collection period. Samples coming to the NHLBI Biorepository are intended for future research and the exact parameters for future testing are not known. Therefore, meticulous record-keeping is essential to ensure that all relevant variables are captured. At a minimum these variables must include:

   - Subject ID
   - Visit identifier

- Date/Time of Collection
- Storage temperature between collection and processing
- Date/Time processing initiated
- Vial ID
- Preserved Material Type
- Tube type and/or preservative used
- Volume or Quantity
- Date/Time Frozen
- Vial Comments *(e.g., sample condition, indications of hemolysis, etc.)*
- Storage Temperature
- Stored vial location

An example of a sample collection record-keeping template may be found here

Example Sample Collection Record-Keeping Template

Additional variables may be appropriate to the research being conducted and to the consideration of the suitability of collected biospecimens for future studies, such as:

- Patient condition at the time of collection *(e.g., "fasting")*
- The specific SOP used for processing
- Deviations or non-conformances from usual practice
- Staff performing tasks

4) Appropriate labeling procedures must be developed. These include the characteristics of the label stock used as well as the format and content of the information on the printed label.

Labels must be tested to ensure that they will adhere to the vials and remain legible over time. These tests must include the temperatures to which the vials will be exposed and common chemicals that are used in the laboratories where the samples will be processed and tested.

All samples submitted to the NHLBI Biorepository must be labeled with a unique identifier (accession number) in both human readable and bar-code format. A brief description of the specimen material type in the vial (i.e., serum or PBMC) may also appear on the vial label to assist laboratory personnel during processing. No other information (i.e., donor identifiers, dates, volumes, etc.) may be present on the vial label and no information may be handwritten on the vial label.

The database used by the NHLBI repository utilizes an identifier called a BSI ID that is unique to each vial. The BSI ID is made up of two components: an accession number that is unique to the draw of a participant (Sample ID), and a sequence number that is unique to the vial within that draw. It is preferred, but not required, for studies to use the BSI ID as the unique identifier on each vial. Below is an example of the standard label used by the NHLBI Repository:

AA123456 789

Plasma

In this example, AA123456 is the Sample ID and 789 is the sequence number; all vials created from a single collection would be labeled with the same Sample ID, but the sequence number on each vial generated from that collection would be unique. Assistance to applicants will be provided in the design of appropriate label sets. An example full BSI label set can be found here: https://biolincc.nhlbi.nih.gov/static/guidelines/label_set.pdf

5) A data collection/data management plan must be in place. This plan must address both clinical data collection/management and informatics related to biospecimen data management, inventory control and biospecimen tracking.

The data collection/data management plan must specify the data elements to be collected, the technology to be used to electronically record and store these data, who will be performing data collection, whether a data coordinating center will be used, and the plans for data quality assurance/quality control (QA/QC).

All biospecimen collections must have at least minimal information associated with each vial. The components of this minimal dataset are known as vial characterization data, and their specific elements will vary between studies. Examples might include donor/recipient status, visit identifier, gender, preservation/processing information, etc. Vial characterization data are only distributed in tandem with requested biospecimens. However, the data quality/data assurance procedures used for the generation of vial characterization data must be addressed in the submitted QA/QC plan.

A linkage file must be maintained which clearly links the accession number on each vial within the biospecimen collection to its participant source, including subject ID, date of collection and specimen material type as minimum requirements. For an example linkage file can be found here: https://biolincc.nhlbi.nih.gov/static/guidelines/linkage_file.doc. Because most NHLBI-sponsored research studies will also provide study datasets to the NHLBI Data Repository, researchers should review Section 3.1 - Preparing And Submitting Data Repository Datasets. Whether or not a study is destined to participate in the NHLBI Biorepository, it is strongly recommended that any personal-identifier data elements first be carefully considered in regards to the necessity of their inclusion. Those elements which must be collected should be maintained in secured and separate datasets from the main clinical data elements, utilizing a coded linking file which is maintained as yet another secured and separate dataset.

6) QA/QC plans that are specific to the research to be conducted must be in place. Formalized QA/QC policies are developed at collection and storage sites to minimize circumstances that could adversely affect scientific results. The policies, also known as the Quality Management System (QMS), are customized for the intended and potential uses of biospecimens that will be collected and stored. Researchers may wish to consult the following sources for information regarding Best Practices relating specimen handling:

National Cancer Institute (NCI) Best Practices for Biospecimen Resources (June 2007)
http://biospecimens.cancer.gov/practices/

ISBER Best Practices for Repositories (2008) http://www.isber.org/ibc.html

7) Collections must conform with ethical, legal and policy requirements. An informed consent document must be used which is specific to the future use of biospecimens in the context of a shared biospecimen resource. It is strongly encouraged that new studies employ a separate consent for biospecimens which are intended to become a shared resource. Information on sources for biospecimen ethical issues is available at http://bioethics.od.nih.gov/withinnih.html

   Submission of all informed consent documents, including site-specific variations, is a requirement for application review. Discussions of issues related to informed consents for biospecimen collections for shared resources may be found at the following sites:

   National Cancer Institute (NCI) Best Practices for Biospecimen Resources (June 2007) http://biospecimens.cancer.gov/practices/

   ISBER Best Practices for Repositories (2008) http://www.isber.org/ibc.html

   A study template may be sent for the initial application. Site-specific consent documents should be reviewed by the parent study group and must be supplied to BioLINCC prior to the shipment of biospecimens to the NHLBI Biorepository. Data associated with tiered consent must be collected and linked to the biospecimen inventory.

3.2.4 OVERVIEW OF THE NEW BIOLOGIC SPECIMEN COLLECTION APPLICATION PROCESS

The BioLINCC website https://biolincc.nhlbi.nih.gov is the interface for the application to submit new biospecimen collections.

STEP 1 – REGISTRATION ON THE BIOLINCC WEBSITE:
Studies which are considering whether to apply for storage of their biospecimen collection at the NHLBI Biorepository should register their study on the BioLINCC site https://biolincc.nhlbi.nih.gov as early as possible. The information collected at registration includes basic identifiers such as the protocol name and acronym and contact information for the Network/RFA Group, Principal Investigator, principal study contact, and NHLBI Program. The registration form also collects information on:

- The current status of the study (in planning, in process or completed) and the actual or anticipated study collection start and end dates.
- Very basic information on the study itself, such as a brief summary of the protocol, the number of participating centers, the use of central data management and/or specimen processing labs, the target/actual accrual, and the anticipated number of study biospecimen collection visits per participant.
- Transfer of the collection to the NHLBI Biorepository (bulk relocation at the end of the clinical study or incremental shipments during the study).

Researchers should be aware that, generally speaking, the NHLBI Biorepository will no longer support ongoing incremental submissions of biospecimens but will instead only accept collections which are transferred as a bulk relocation at the end of the research study.

Exceptions may be granted in the case of small unique collections and in the case of emergent collections with exceptional public health implications. Most studies, especially large studies with multiple research centers are strongly encouraged to plan and budget for central labs for specimen processing and storage throughout their active collection phase.

Researchers wishing to apply for incremental submissions must provide justification, and should be aware that this type of submission is subject to ongoing interim quality assurance reviews. Failure to resolve issues identified during interim reviews of incremental submissions may result in the termination and removal of such collections from the NHLBI Biorepository.

The information collected in the registration form is used by BioLINCC to determine the appropriate next actions, and the researcher, the study NHLBI Program/Project Officer and the NHLBI Biorepository Project Officer will be contacted via email with this information. A link to the registration form is provided here: https://biolincc.nhlbi.nih.gov/register/.

STEP 2 – APPLICATION FOR BIOSPECIMEN STORAGE:
The researcher will be contacted by BioLINCC to submit application materials via the BioLINCC website following successful completion of the registration process.

Materials required for all applications include:
1. The application form
2. The study protocol
3. Standard Operating Procedures (SOPs) related to biospecimen collection, processing, storage and transfer
4. The worksheet and forms used for record-keeping of collection and processing variables related to sample collection
5. The biospecimen labeling plan
6. The data collection/data management plan
7. The quality control/quality assurance plans
8. All Informed Consent templates

Additional materials required for applications for incremental transfer:
1. Justification for incremental transfer rather than bulk relocation at the end of the study.
2. Documentation that the technical requirements for incremental transfer can be met
3. A plan for the review and approval of biospecimen requests in the proprietary period. The plan must include procedures for reviewing the distribution of the last aliquot for a subject and for complying with any research use restrictions in the Informed Consent document.

Submitted materials will be reviewed by NHLBI Biorepository, BioLINCC and BioROC staff to determine whether the intrinsic value, technical and ethical requirements appear to be addressed, and feedback will be provided, as appropriate, regarding areas of potential improvement. If the requirements cannot be met, the application may be terminated at this time.

The review process for applications for incremental transfer will include a review of the feasibility of this transfer type. In addition, incremental biospecimen shipments will be monitored by the NHLBI Biorepository and the BioLINCC staff. Shipping will be put on hold if the specimen manifest discrepancy rate is >5% or if there are other biospecimen quality assurance

issues. If these issues cannot be resolved in a timely manner, the collection may be returned or discarded after consultation with the submitting researcher. Repository IRB approval is required before initiation of incremental shipping.

A summary of the review will be provided to the applicant. The summary will include the BioROC decision and details of the accepted collection plan, including details of the proposed study collection and the transfer and distribution of the biospecimens. In general, parent studies will be expected to assist with the cost of transferring biospecimens to the Biorepository and should include shipping costs in the parent study budget.

Researchers who participate in a pre-review of their proposed study methodology as it relates to biospecimen and data collection are eligible for custom cryolabels which are pre-printed in the required format and provided to the researcher at no charge.

STEP 3 - FINAL STATUS REVIEW:
Upon study completion, the researcher will be asked to submit the final study protocol, SOPs, Informed Consent documents and other relevant materials that may have undergone revisions from the initial Application, or to verify that the previously submitted documents have not changed. In addition, final clinical data sets and associated documentation as related to biospecimens in the collection will be requested at this time. A summary of the study collection materials and associated data will be prepared by BioLINCC, and a final confirmatory review of collection acceptance will be made by BioROC. A summary of the review will be provided to the applicant.

If the study collection is accepted by BioROC, the application will be reviewed by the NHLBI Biorepository IRB. (This step does not apply to Incremental Transfer studies because they will have an existing IRB approval).

If the study collection is deemed Not Accepted by BioROC, the researcher will be provided with comments on whether modifications to the submitted materials might lead to eventual acceptance. Collections with inherent deficiencies in biospecimen collection, processing, or storage, or with Informed Consents which were not explicit regarding the potential for shared biospecimen banking will not be accepted. Collections which have been transferred under the Incremental Shipment plan but which are found to be unacceptable upon final review will be returned or discarded after discussion with the researcher.

STEP 4 – STUDY COLLECTION ADDED TO BioLINCC:
At this time, final arrangements will be made with the NHLBI Biorepository for the relocation of biospecimens. After transfer, the collection will be activated on the BioLINCC shared resources website.

Studies should budget to assist with the cost of the biospecimen transfer at the end of the study.

Definitions

Aliquot	A process wherein a specimen is divided into separate parts which are typically stored in separate containers as individual samples. The term aliquot may also be used as a noun to denote a single sample (ISBER 2008 Best

	Practices for Repositories)
Ancillary Study	An additional or secondary trial that was not part of the original study design.
Anonymized Biospecimens	Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification. (Guidance for Industry: E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. FDA April 2008).
Authorized Institutional Business Official	Someone in a senior position who is authorized to commit to procurements or the allocation of resources. The particular titles vary widely between institutions.
Best Practices	Standard operating procedures that are considered state-of-the-science consistent with all applicable ethical, legal, and policy statutes, regulations, and guidelines. (NCI Best Practices working definition)
BioLINCC	Coordinating center that manages the operational activities of both the NHLBI Biorepository and the Data Repository. It also provides a single web-based user interface to give interested researchers an access point to both resources.
Biorepository	An organization, place, room, or container (physical entity) where biospecimens are stored. In the context of the NCI Best Practices, only biorepositories containing human specimens collected with an intention to use them for research purposes (research biorepositories) are addressed. The physical structure, policies, and the biospecimens and data contained within it are defined collectively as a biospecimen resource, defined below (NCI Best Practices working definition).
Biorepository Informatics System	The software, hardware, written documents, support, and training that are necessary to annotate, track, and distribute biospecimens within a biorepository or biorepositories.
BioROC	The committee responsible for oversight of the collections and determining whether new collections meet the criteria for inclusion in the repositories.
Biospecimen	A quantity of tissue, blood, urine, or other biologically derived material. The NHLBI Biologic Specimen Repository stores human biospecimens. Portions or aliquots of a biospecimen are referred to as samples (NCI Best Practices working definition).
Biospecimen Resource	A collection of human biological specimens and associated data for research purposes, the physical entity where the collection is stored, and all relevant processes and policies. Biospecimen resources vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer (NCI Best Practices working definition).
BSI	A computer system used to manage and maintain biospecimen inventories (Also see Biorepository informatics system)
Bulk Relocation	This is the process for preparing and submitting biospecimens to BioLINCC when the intent is to transfer specimens in bulk at the close of the study (see Incoming Collection Workflow (Bulk Relocation)

	https://biolincc.nhlbi.nih.gov/flow_primary/). This is the preferred process for submission of biospecimen collections to BioLINCC.
Business Plan	A formal statement of a set of business goals, the reasons why they are believed attainable, and the plan for reaching those goals. It may also contain background information about the organization or team attempting to reach those goals. (Wikipedia)
Clinical Data	Factual information (as measurements or statistics) or observations used as a basis for reasoning, discussion, or calculation pertaining to clinical trials, diagnosis, or treatment (NCI Best Practices working definition).
Clinical Research	Patient-oriented research, including epidemiologic and behavioral studies, outcomes research, and health services research. Patient-oriented research is research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) in which a researcher directly interacts with human subjects. It includes research on mechanisms of human disease, therapeutic interventions, clinical trials, and development of new technologies, but does not include in vitro studies using human tissues not linked to a living individual. Studies falling under 45 CFR 46.101(a) (4) are not considered clinical research for purposes of this definition. (NIH grants glossary, http://grants.nih.gov/grants/glossary.htm#C)
Clinical Trial	A biomedical or behavioral research study of human subjects designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. (NIH grants glossary, http://grants.nih.gov/grants/glossary.htm#C)
Code of Federal Regulations (CFR)	The codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government. (GPO Access, http://www.gpoaccess.gov/cfr/index.html). The Federal Register is the official daily publication for rules, proposed rules, and notices of Federal agencies and organizations, as well as executive orders and other presidential documents. (GPO Access, http://www.gpoaccess.gov/fr/index.html)
Coded	Means that (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens. (Office for Human Research Protections, Guidance on Research Involving Coded Private Information or Biological Specimens, http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf) Coded biospecimens are labeled with at least one specific code and do not carry personal identifiers. a) Single-coded biospecimens. Biospecimens are labeled with a single code and do not carry any personal identifiers. It is possible to trace the biospecimens back to a given individual. b) Double-coded biospecimens. Biospecimens are initially labeled with a

	single specific code and do not carry any personal identifiers. They are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the biospecimens back to an individual by using both coding keys. (Guidance for Industry: E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. FDA April 2008).
Collection	1. The act of gathering things together; having been brought together in one place (NCI Thesaurus). 2. An accumulation of objects gathered for study, comparison, or exhibition (Merriam-Webster Dictionary)
Confidentiality	The state of having the dissemination of certain information restricted. (Black's Law Dictionary) See Privacy.
Custodianship	The caretaking responsibility for a biospecimen collection, including management and documentation, as well as the right to determine the conditions under which the specimens are accessed and used. (NCI Best Practices working definition)
Data	Factual information derived from scientific experiments or diagnostic procedures organized especially for scientific analysis in a numerical form suitable for digital transmission or processing by computer, digitally transmitted or processed and used as a basis for reasoning, discussion, or calculation. (NCI Best Practices working definition)
Data set	A data file or a collection of interrelated data records (also see Study Data Set)
Disposal	Systematic destruction of medical waste and other biohazardous waste. (NCI Best Practices working definition)
Distribution	A process that includes receipt of request for specimens, selection of appropriate specimens, and final inspection, in conjunction with subsequent shipment and delivery of specimens to another repository, specimen collection center, or laboratory. (ISBER 2008 Best Practices for Repositories).
Human Subject	A living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information. (45 CFR § 46.102(f))
Incremental Biospecimen Transfer	This is the process for preparing and submitting biospecimens to BioLINCC when the intent is to transfer specimens over the course of the study (see Incoming Collection Workflow (Incremental) https://biolincc.nhlbi.nih.gov/flow_alternate/). This practice is discouraged and will only be granted under exceptional circumstances.
Informed Consent	The legally effective consent of the human subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence (45 CFR §

	46.116(a)).
Institutional Review Board (IRB)	Any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of the research and to conduct periodic review of such research. (ISBER 2008 Best Practices for Repositories)
Label	Any written, printed or graphic material on or affixed to a specimen container or package (ISBER 2008 Best Practices for Repositories)
Linkage File	A list that associates biological samples with the relevant clinical data. It is used to match the IDs that were used for the biospecimens to those that were used for the clinical records for all of the study subjects.
Material Transfer Agreement	Generally utilized when any proprietary material is exchanged, and when the receiving party intends to use it for his/her own research purposes. Neither rights in intellectual property nor rights for commercial purposes may be granted under this type of agreement. (NIH Office of Technology Transfer, http://ott.od.nih.gov/cradas/model_agree.aspx)
Open Period	The period following the close of the proprietary period (see definition below). The NHLBI Repository Allocation committee is solely responsible for distribution and release of data and/or biospecimens for studies and collections in the Open Period.
Parent Study	1. The clinical study collecting the data and/or biospecimens. 2. The principal or primary study (see ancillary study).
Privacy	Freedom from intrusion of others into one's private life (Merriam Webster); the right to be let alone (Black's Law Dictionary)
Processing	Any procedure employed after specimen collection but prior to its distribution, including preparation, testing, and releasing the specimen for inventory and labeling. (ISBER 2008 Best Practices for Repositories)
Proprietary Period	A period of time in which biospecimens and/or clinical data are stored in the NHLBI repository prior to their availability for sharing according to the NHLBI Data Set sharing policy timeline. During the Proprietary Period, the BioLINCC website directs requesting researchers to the Parent Study for additional information on data and biospecimens, because that information may not yet be available to BioLINCC.
Protected health Information (PHI)	Individually identifiable information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. (45 CFR § 160.103) (See HHS Office for Civil Rights – HIPAA, http://www.hhs.gov/ocr/hipaa/)
Repository Allocation Committee (RAC)	The committee responsible for determining if requests for datasets and/or biospecimens meet the criteria for use in research studies. They are also responsible for assuring that critical last vials are not removed without valid scientific justification.
Repository	An entity that receives, stores, processes and/or disseminates specimens, as needed. It encompasses the physical location as well as the full range of activities associated with its operation. It may also be referred to as a biorepository (ISBER 2008 Best Practices for Repositories)
Research	Systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR § 46.102(d)).

Research Resources	Biospecimens, study datasets, or both.
Retrieval	The removal, acquisition, recovery, harvesting, or collection of specimens (ISBER 2005).
Sample	1. Portions of biospecimens (NCI Best Practices working definition). 2. A single unit containing material derived from one specimen (ISBER 2008 Best Practices for Repositories).
Shipping Manifest	A description of the contents of the shipped package (ISBER 2008 Best Practices for Repositories). In the context of the NHLBI Biorepository, an electronic shipping manifest must be sent prior to shipment. A hard copy of the shipping manifest must be included with the shipment.
Specimen	See Biospecimen
Specimen Characterization Data	The quantitative or qualitative information linked to the biospecimen which may include: type of specimen (i.e., plasma, urine), type of fixative or additives, some demographic data, and laboratory test results.
Standard Operating Procedure (SOP)	An established or prescribed method to be followed routinely for the performance of designated operations or in designated situations (Merriam-Webster Dictionary)
Standard Operating Procedures Manual	A group of standard operating procedures (SOPs) detailing specific policies of a repository and the procedures required to be used by the staff/personnel. (ISBER 2008 Best Practices for Repositories).
Study Collection	The accumulated biospecimens collected by a clinical study. (NHLBI working definition)
Study Data Set	The information collected and recorded from study participants through periodic examinations and follow-up contacts, not including original specimens or images.
Tissue	An aggregate of cells with different specialized characteristics that are organized anatomically, usually in the fixed framework of an organic matrix. The architectural organization that is maintained contributes to the performance of the specific collective function. Tissues are parts of organs. The term tissue is most often referred to in the context of solid tissue, as originating from a solid organ; however, tissue also can be defined broadly to include collections of cells and the extracellular matrix and/or intercellular substances from bodily fluids such as blood (NCI Best Practices working definition).

Acronyms and Abbreviations

BioLINCC	Biologic Specimen and Data Repository Information Coordinating Center
BioROC	BioRepository Organizing Committee
BSI ID	Biospecimen inventory identifier
DBDR	Division of Blood Diseases and Resources
DPPS	Division of Prevention and Population Sciences
NHLBI	National Heart, Lung, and Blood Institute
QA	Quality Assurance
QC	Quality Control
RAC	Repository Allocation Committee
RMDA	Research Material Distribution Agreement
SOP	Standard Operating Procedure